Exhibit 6

Overview

1. **Behavioral Studies**
   - **1.1. *Mitragyna speciosa* and *Salvia divinorum***
     - 1.1.1. Chemistry and finger printing
     - 1.1.2. Animal studies
     - 1.1.3. Pharmacokinetics
     - 1.1.4. Deliverables
   - **1.2. *Sceletium tortuosum***
     - 1.2.1. Chemistry and finger printing
     - 1.2.2. Animal studies
     - 1.2.3. Pharmacokinetics
     - 1.2.4. Deliverables
2. **Hepatotoxic Studies**
   - **2.1. Green Tea**
     - 2.1.1. Aqueous and non-aqueous fractions of green tea on mouse liver
     - 2.1.2. EGCG-induced hepatotoxicity
     - 2.1.3. Are females more susceptible to EGCG induced hepatotoxicity?
     - 2.1.4. Effect of GT and EGCG on HepG2 cells
     - 2.1.5. Deliverables
   - **2.2. Black Cohosh**
     - 2.2.1. Methanol extracts from three *Cimicifuga* species on healthy female mice
     - 2.2.2. Methanol extracts from three *Cimicifuga* species on LPS-induced unhealthy female mice
     - 2.2.3. Aqueous and non-aqueous fractions of *C. dahurica* on mice
   - **2.3. OxyElite Pro (OEP)**
     - 2.3.1. Toxicity of OEP in healthy mice
     - 2.3.2. Toxicity of OEP in heath compromised mice
3. **References**

In-vivo Safety Evaluations for Botanicals of Interest

To address the needs of the FDA on the safety of BDS, Dr. Ikhlas Khan, Scientific Director for the project, consults regularly with the Director of the Division of Dietary Supplement Programs and liaison at CFSAN. The center will continue to exchange information on developed methods, reference materials availability, safety evaluations and project direction with CFSAN. Under this umbrella, priority evaluation was given to botanicals that have displayed an inherent risk based on literature information or reported adverse events. The NCNPR established two in-house preliminary *in-vivo* safety evaluations for botanicals of interest. Initial screens focused on two areas of concern. The first mouse model (Behavioral Studies) measured botanicals for their potential to induce positive reinforcement or cause aversive properties using a conditioned place preference (CPP) paradigm procedure that is commonly used to evaluate drugs for their "addictive" behavior. The second *in-vivo* assay was developed to evaluate the potential hepatotoxicity associated with botanical as measured by a mouse model (Hepatotoxic Studies) where the hepatotoxicity is manifested by elevation of aminotransferases and histopathological features of acute hepatocellular necrosis and/or biliary injury. Both *in-vivo* models will continue to provide significant insight into the safety profile for botanicals that are of concern for public health.

1.0 Behavioral Studies:

One procedure to evaluate a compound's abuse potential is the Conditioned Place Preference (CPP) procedure. This associative learning paradigm is based on the notion that animals prefer environments previously paired with positively reinforcing drugs.[1] It should be noted that compounds that possess unpleasant properties produce Conditioned Place Aversion (CPA) in the paradigm. CPP/CPA, in the traditional use of studying single-entity compounds, may not lend itself well to the study of complex botanical products. Botanicals possess a wide range of constituents that may have antagonistic or synergistic effects that mask or exacerbate liabilities, respectively. Thus, studying only a major constituent or the entire extract alone may fail to identify potential liabilities. One approach is to concomitantly evaluate the full extract, one or more of its fractions and its major constituent(s) in the paradigm. This strategy could reveal antagonistic or synergistic effects within the extract and fraction and more fully characterize constituent liabilities.

Over the past year the Center used this model to evaluate the whole extract, enriched fractions and pure compounds isolated from the following species.

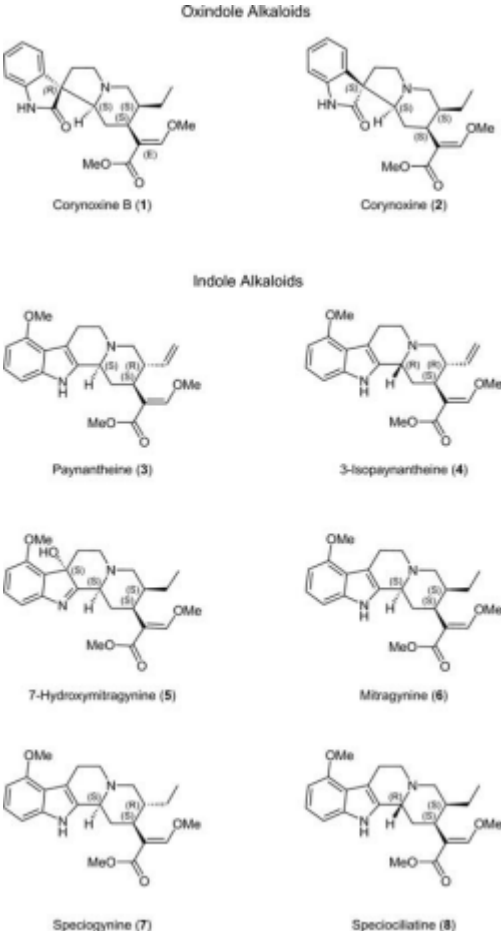
1) *Mitragyna speciosa* and *Salvia divinorum*
2) *Sceletium tortuosum*

1.1 Project-1: *Mitragyna speciosa* and *Salvia divinorum*

1.1.1 Chemistry and Fingerprinting: A new indole alkaloid, 7 -hydroxy-7H-mitraciliatine and a new oxindole alkaloid, isospeciofoleine together with nine known alkaloids were isolated from *Mitragyna speciosa* and characterized by NMR, CD, and MS spectroscopic data analyses. The ^{1}H and ^{13}C NMR spectroscopic data of isospeciofoline, isorotundifoline, paynantheine, and 3-isopaynantheine were also reported for the first time.[2]

A single qualitative LC–QToF-mass spectrometry (MS-MS) method for the separation, characterization and chemical profiling of alkaloids in association with chemometric analysis not only for assessing quality but also for the study of the variations in active constituents among samples of *M. speciosa* was developed.[3]

In addition to LC-MS method, three independent chromatographic methods[4] coupled to two detection systems, GC with MS, supercritical fluid chromatography (SFC) with diode array detection, and HPLC with MS



and diode array detection, were compared for the analysis of mitragynine and other indole and oxindole alkaloids in *M. speciosa* plants.

Figure 1. Structures and stereochemistry of mitragynine and other indole and oxindole alkaloids commonly found in *M. Speciosa*.

1.1.2 Animal studies:

Ethnopharmacological Relevance: Consumer use of botanicals has increased despite, in many instances, the paucity of research demonstrating efficacy or identifying liabilities. The current research employed the place preference/aversion paradigm to characterize the psychoactive properties of *Salvia divinorum* extract (10, 30,100mg/kg), salvinorin-A (0.1, 0.3, 1.0mg/kg), *Mitragyna speciosa* MeOH extract (50,100,300mg/kg), *Mitragyna speciosa* alkaloid-enriched fraction (12.5, 25, 75mg/kg) and mitragynine (5,10, 30mg/kg) in rats.

Material and Methods: Following apparatus habituation and baseline preference scores, male Sprague-Dawley rats were given eight counter-balanced drug versus vehicle conditioning trials followed by a preference test conducted under drug-free states. S(+)-amphetamine (1mg/kg) served as the positive control (inExp.2) and haloperidol (0.8,1.0mg/kg) served as the negative control in both studies.

Results: Rats displayed place aversion to both *Salvia divinorum* and salvinorin-A which exceeded that of haloperidol. Rats showed place preference to mitragynine that was similar to that of S(+)-amphetamine. This CPP effect was much less pronounced with the *Mitragyna speciosa* extract and its fractions.[5]

Conclusions: These findings suggest that both botanicals possess liabilities, albeit somewhat different, that warrant caution in their use.

1.1.3 Pharmacokinetics: The major alkaloids mitragynine, 7-hydroxymitragynine, and mitraphylline are reported to be the central nervous system active alkaloids which bind to the opiate receptors. Even though several therapeutic properties have been reported for these compounds, only limited information is available on the Absorption, Distribution, Metabolism, and Excretion (ADME) properties. We have undertaken to study ADME properties of these compounds and their effect on the major efflux transporter P-glycoprotein, using *in vitro* methods. Additionally, the stability of mitragynine, 7-hydroxymitragynine and mitraphylline were subjected to Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF).[6] All three compounds exhibited high plasma protein binding (> 90%) determined by equilibrium dialysis. Mitragynine and 7-hydroxymitragynine inhibited P-glycoprotein with EC_{50} values of 18.2 ± 3.6 µM and 32.4 ± 1.9 µM, respectively, determined by the calcein-AM fluorescent assay, while no inhibition was seen with mitraphylline. These data suggest the possibility of a drug interaction if mitragynine and 7-hydroxymitragynine are co-administered with drugs that are P-glycoprotein substrates.

1.1.4 Deliverables:

[1] Chemistry, Fingerprinting, Analytical Methods, Pharmacokinetics and Behavior Studies of *Mitragyna speciosa* (Kratom)

[2] Five peer-reviewed publications.

1.2 Project-2: *Sceletium tortuosum*

Sceletium tortuosum, belonging to the family Mesembryanthemaceae, is an indigenous South African herb. It is commonly called Kanna, or Channa.[7] Traditionally, the plant is consumed in the form of a tincture, chewing dried leaves or smoking it is widely used in the treatment of Central Nervous System (CNS) related disorders such as anxiety, depression, and stress.[8] *Sceletium* extracts are also widely used throughout the world as an herbal supplement in the treatment of anxiety and stress. A recent clinical study with the plant extract (Zembrin) showed that it has a very good anxiolytic potential in humans by combined inhibition of serotonin (5-HT) reuptake and phosphodiesterase-4 (PDE4).[9]

1.2.1 Chemistry:

As a part of phytochemical investigation, we have isolated several known and unknown alkaloids from *S. tortuosum*. Noticeably, these marker components will assist us in authentication, identification and development of analytical methods for *S. tortuosum* and its principle alkaloid components. The majority of these findings have not yet been published; however, they will be reported shortly.

1.2.2 Animal studies: [10]

Ethnopharmacological relevance: Broad historical and current uses in addition to diverse activity on CNS targets may make *S. tortuosum* a useful therapeutic agent in a variety of clinical settings.

Aim of the Study: This study sought to more broadly characterize activity of *S. tortuosum* and mesembrine in a number of common, rodent-based assays that model nociception, depression, anxiety, ataxia, and abuse liability.

Male Sprague-Dawley rats were administered *Sceletium tortuosum* extract products and behavioral responses were evaluated in the conditioned place preference (CPP), hot plate, forced swim, elevated plus, and rotarod tests.

Conclusions: S. tortuosum did not cause preference or aversion in CPP. Mesembrine appears to have analgesic properties without abuse liabilities or ataxia (loss of coordination). The *S. tortuosum* fraction has antidepressant properties but does produce ataxia. The ataxia may limit its usefulness as an antidepressant unless the antidepressant activity is associated with one constituent and the ataxia is associated with a separate constituent.

1.2.3 Pharmacokinetics:

Despite the wide use and reports in literature confirming the pharmacological activities of *Sceletium* extract, there are no in vivo pharmacokinetic or ADME studies of its active ingredients, mesembrine and mesembrenone. To address these issues, we have undertaken development of analytical method for identification and application to intravenous plasma pharmacokinetics of mesembrenone and mesembrine in mouse. Currently, these studies are ongoing in our lab, the outcome and results will be as soon as possible.

1.2.4 Deliverables:

[1] Chemistry, Fingerprinting, Analytical Methods, Pharmacokinetics and Behavior Studies of *Sceletium tortuosum* (Kanna)
[2] Posters and Publications

2.0 Hepatotoxic Studies:

Initial *in-vivo* hepatotoxicity evaluations of (-)-Epigallocatechine-3-gallate (EGCG), a major component in green tea products, at high doses can lead to mild liver injury and under febrile conditions can cause severe liver injury. Under this model, scientists from the NCNPR are continuously engaged in identification and assessment of potential hepatic botanicals or dietary supplements. For the past year, the following species/products were undertaken for hepatotoxic studies.

1) Green Tea
2) Black Cohosh
3) OxyElite Pro

2.1 Project 1: Green Tea Supplement

Concerns about the safety of natural products are emerging worldwide. Green tea (GT) is not only one of the most widely used drinks around the world, but is also used for the treatment of various ailments. Mega doses of GT are now available commercially in capsular form. We embarked upon a program to study the safety of these natural supplements in laboratory animals as well as in cell culture system. The following briefly highlights the results obtained from the studies conducted at National Center for Natural Products Research.

2.1.1 Study # 1:[11]

The first set of experiments were conducted using different fractions and extracts of GT (aqueous and methanolic extracts, phenolic and non-phenolic fractions of GT). In these experiments we studied the effect of different doses (500, 1000 and 2500 mg/kg body weight) on mouse liver.

Outcomes:

[1] The results confirmed that consumption of the aqueous extract of GT (up to 2500 mg/kg) does not cause any untoward effect.

[2] Non-aqueous fractions (methanolic) of GT in higher doses (1000 mg/kg and above) caused liver toxicity.

2.1.2 Study # 2:[11, 12]

Safety concerns on the consumption of EGCG, the main polyphenol of GT, are emerging. Many studies and case reports implicated EGCG to be hepatotoxic. The underlying conditions of EGCG-induced hepatotoxicity were a point of interest in our labs. To this end, we conducted a second set of experiments to study the effect of EGCG on mouse liver in either normal conditions and under the influence of lipopolysaccharide (LPS) as an inflammagen.

Outcomes:

[1] Under normal conditions, consumption of EGCG up to 750 mg/kg may be safe, but higher doses can cause hepatotoxicity.

[2] Under inflammatory conditions (fever) EGCG administration showed hepatotoxicity even with lower dose (750 mg/kg).

2.1.3 Study # 3: “Are Females More Susceptible to EGCG Induced Hepatotoxicity?”

A search of the literature indicated that consumption of EGCG supplements is more prevalent among females compared to males. This fact is due to the greater demand by female for weight control supplements. Statistics show that the percentage of obesity is much higher in females than in males. Based on these facts we conducted a third set of experiments to compare the effect of EGCG, under the influence of LPS, on female and on male mice.

Outcome:

Data showed that hepatic injury in female mice was more severe than those of male mice; based on clinical chemistry and histopathology of livers from both groups.

2.1.4 Study # 4:[12, 13]

In an attempt to study the effect of GT and EGCG on human liver cells, we conducted another set of experiments on HepG2 cells. Although these are human hepatoma cells, they are considered to be a relatively viable model for bioavailability and toxicity studies.

Outcomes:

[1] Green tea aqueous extract (without LPS) was not deleterious to HepG2 cells, while under the influence of LPS, GT aqueous extract showed hepatocellular toxicity.

[2] Green tea aqueous extract even at higher doses (up to 500 mg/mL) did not cause oxidative stress. However, under inflammatory stress conditions caused by LPS it caused oxidative stress which in turn may contribute in the hepatocellular toxicity.

Study # 5:[13]

Another study was conducted to evaluate the effect of EGCG on HepG2 cells. This study showed that EGCG in higher concentrations, without LPS, can behave as a pro-oxidant. Whereas, LPS induced inflammatory conditions made lower concentrations of EGCG to behave as a pro-oxidant.

Conclusions: Consumption of water extract of GT even at high doses is relatively safe under normal conditions. Under inflammatory conditions (fever), consumption of high doses of GT can be hepatotoxic. In addition, consumption of high doses of EGCG even under normal conditions can cause

adverse effects. Under inflammatory conditions, consumption of even lower doses of EGCG can show hepatotoxicity.

2.1.5 Deliverables:

[1] Hepatotoxic properties of water extract of Green Tea and its principle phenolic component, EGCG.
[2] Four peer-reviewed publications

2.2 Project 2: Liver Toxicity of Black Cohosh in Mice

Black Cohosh (BC) (*Cimicifuga racemosa*) has been widely used for the treatment of menopausal symptoms. Sporadic cases of liver toxicity with BC have raised concerns of its safety. Regulatory agencies in different countries have shown concern about the potential association between black cohosh and hepatotoxicity. It is also worth noting, that predisposing conditions that lead to hepatotoxicity in users of BC product is an important factor, but has been frequently overlooked in the clinical reports.

2.2.1 Study # 1:

This study examined the effects of the intragastric (IG) administration of methanol extracts from three BC species (*Cimicifuga racemosa, Cimicifuga foetida* and *Cimicifuga dahurica*) on female mice for 10 days. Mortality, body and liver weights, and blood levels of alanine transaminase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN) were determined for assessment of liver injury.

Outcome:
The results showed no mortality in mice administered daily doses of 75, 150, 300, 600, 1,200 mg/kg for 10 days. Body: liver weight ratio remained comparable to control animals. Blood biochemical parameters did not show any significant alteration indicating no effect on liver.

2.2.2 Study # 2:

In an attempt to determine the effect of BC under health compromised condition, mice were injected a single dose of 6.0 mg/kg LPS intraperitonealy on day 1, followed by daily itragastric doses of methanol extracts of three BC species (*Cimicifuga racemosa*, *Cimicifuga foetida* and *Cimicifuga dahurica*). This was continued for 10 days.

Outcomes:
[1] No untoward effect was observed with *Cimicifuga racemosa*, *Cimicifuga foetida* at doses 300, 600, 1,200 mg/kg. However, *Cimicifuga dahurica* at higher doses (1000 and 1,200 mg/kg) caused 67% and 87% mortality in mice, respectively, within three days post treatment.
[2] Mice treated with LPS and *Cimicifuga racemosa*, *Cimicifuga foetida* did not show any elevation in blood ALT or BUN suggesting no liver toxicity.
[3] Mice treated with LPS and *C. dahurica* at doses 300, 600 and 800 mg/kg/day did not show any change in ALT or BUN. However, mice given LPS and *C. dahurica* at doses 1000 mg/kg and 1200 mg/kg showed significantly elevated ALT (3-4 fold respectively) and BUN (approximately 6 fold) indicating liver toxicity.

2.2.3 Study # 3:

The next part of this study was to determine which fraction of *C. dahurica* contained toxic product that would cause liver toxicity in mice. The extract was further fractionated into organic and aqueous fractions (Fraction I, soluble in organic solvent; Fraction II, soluble in water). Mice were sensitized with LPS (6.0 mg/kg IP) on day 1, followed by daily intragastric administration of Fraction I or Fraction II for 10 days. As a positive control, one group of mice was given whole extract of *C. dahurica* daily, with a single dose of LPS intraperitonealy on the first day.

Outcomes:

[1] Results showed that Fraction I at doses 200, 400 and 600 mg/kg caused 100 % mortality within 3 days.

[2] Treatment with Fraction I caused 3-4 fold increase in blood ALT and 4-6 fold increase in BUN, suggesting liver toxicity.

[3] Treatment with Fraction II did not cause any significant change in ALT or BUN. No mortality was observed in mice treated with Fraction II.

Conclusions:

In summary the three BC species (*Cimicifuga racemosa*, *Cimicifuga foetida* and *Cimicifuga dahurica*) exhibited no significant effect on liver in healthy mice. However, under health compromised condition (inflammatory state/LPS treatment) the methanol extracts of *Cimicifuga dahurica* resulted in liver toxicity and mortality. From these preliminary results, we concluded that *Cimicifuga racemosa* and *Cimicifuga foetida* spp. of black cohosh did not cause liver toxicity even under inflammatory stimulus. In contrast, *Cimicifuga dahurica* at high doses (1000 mg/kg and 1200 mg/kg) caused liver toxicity under health compromised condition such as inflammation or fever. Further bioassay guided fractions indicated organic extract of *C. dahurica* showed significant liver injury and mortality in animals that are presensitized with LPS. Even at lower doses (>200 mg/kg), the 100 % mortality within 3 days warrants further phytochemical investigations. It may be necessary to isolation all of the major components and assay them individually to understand the hepatotoxic nature of component derived from *C. dahurica*. The details of phytochemical investigations, *invivo* data and all other results will be reported in due course.

2.3 Project 3: Liver Toxicity of OxyElite Pro in Mice

OxyElite Pro (OEP) was one of the most popular weight loss supplements; however it is currently withdrawn from the market. According to the manufacturer, OEP increased the user's metabolic function, and burned calories even while consumer at rest. Additionally, the manufacturer claimed that OxyElite Pro was designed to suppress appetite, increase energy, and improve mood. Reports of deaths in consumers of OEP have been reported. Of the 56 cases identified, 22 were hospitalized, of which two had to undergo liver transplant and one died.

2.3.1 Study #1:

We initiated this study to assess liver toxicity of OEP in healthy mice. Capsular contents of OEP were dissolved in 10% DMSO and 10% Tween 80 and water to give a homogenous suspension. After overnight fasting, different groups of mice were administered intragastric different doses of OEP ranging from (31.3 to 2000 mg/kg) daily for 7 days. Blood was collected at the end of the experimental period and liver (ALT, ALP, BUN) parameters were assessed.

Outcome:

Higher doses of OEP (1000 mg/kg and 2000 mg/kg) caused 100% mortality in mice within 6 hours post treatment. No mortality was observed in mice given OEP up to 500 mg/kg per day for 7 days. The surviving mice did not show any change in blood ALT, ALP or BUN. No change in body weights was observed in these animals.

2.3.2 Study #2:

This study was designed to assess the toxicity of OEP in heath compromised mice. These mice were sensitized with a single dose of 6 mg/kg LPS intraperitonealy, followed by daily intragastric doses (31.3 to 500 mg/kg) of OEP. A group of mice was treated with vehicle and another group was given LPS IP followed by intragastric administration of vehicle.

Outcome:

No mortality was observed in health compromised mice given OEP up to 250 mg/kg. However, 500 mg/kg of OEP caused 100% mortality in these mice within 6 hours post treatment. The surviving groups of mice (doses ranging from 31.3 to 250 mg/kg) did not show any change in blood ALT, ALP or BUN.

Conclusion:

OxyElite Pro caused acute mortality at higher doses (above 500 mg/kg) within 6 hours after its administration in healthy and health compromised animals. In the surviving animals (both healthy and health compromised) liver enzyme levels did not show any change suggesting no association of liver toxicity with OEP. The results and other findings associated with OEP will be reported in due course.

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